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to the ERGIC, from which they trigger unabated type I IFN expression. The reason for this constitutive STING translocation to the ERGIC remains unclear; however, as the authors suggest, it is possible that these mutations disrupt the interaction of STING with an ER-resident retention signal that normally prevents the exiting of STING toward the ERGIC in the absence of stimulation. Interestingly, these STING mutants were not translocated to the above-mentioned punctate structures, and they were also largely resistant to degradation. While the latter phenomenon could be explained by the lack of an additional cGAMP signal that seems to be required to facilitate STING degradation (Konno et al., 2013), the authors furthermore show that additional cGAS activation does not initiate the decay of this type of STING mutants. Thus, it appears that a special structural feature of activated, wild-type STING at the ERGIC is required to allow its exit from this compartment for subsequent degradation. In this regard it should be informative to further dissect the mechanisms that facilitate STING transport beyond the ERGIC.

Collectively, the data provided by the new study assign an important role to the ERGIC in STING signaling, adding this unique organelle to the ever-growing list of subcellular compartments that serve as platforms for the initiation of anti-microbial signal transduction. Further dissection of STING trafficking may inform the design of specific therapeutic strategies, geared at the inhibition of STING in the context of sterile inflammatory conditions.

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Dectin-1 Exerts Dual Control in the Gut

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Dectin-1, a β-glucan receptor, contributes to host anti-fungal defense. In this issue of *Cell Host & Microbe*, Tang et al. (2015) show that suppressing Dectin-1 signaling protects mice from experimental colitis by decreasing anti-microbial peptide production, which allows overgrowth of *Lactobacilli* and triggers T regulatory cell expansion in the gut.

Mammalian gastrointestinal (GI) tract is colonized with diverse commensal microbial communities consisting of bacteria, fungi, and viruses. The host mucosal immune system has evolved to tolerate and control this complex ecosystem while ensuring responses against invading pathogens. Deficiencies in genes involved in key innate and adaptive immune pathways often lead to disorders characterized by intestinal manifestations and loss of microbial diversity, or so called dysbiosis. Many of these pathways play a role in the interaction with bacteria and viruses. Recent studies have shown that deficiencies in genes encoding factors involved in anti-fungal immunity can also contribute to diseases targeting the mammalian GI tract (Underhill and Iliev, 2014). The fungal counterpart (mycobiota) of the intestinal microbiota has attracted scientific attention as a possible disease component during these deficiencies.

Among different antifungal receptors, Dectin-1 has been extensively studied for its important role in fungal phagocytosis, killing, and cytokine response. Dectin-1 is a transmembrane receptor that recognizes fungal β-glucan (Taylor et al., 2007). Mice deficient in Dectin-1 are highly susceptible to invasive fungal disease due to decreased ability of phagocytes to sense, kill, and respond to *Candida* (Taylor et al., 2007). This predisposition, however, is dependent on the fungal strain suggesting that some fungi are able to more efficiently mask cell wall β-glucans and become invisible to Dectin-1. In addition to its role in systemic protection against fungi, there is sufficient evidence that Dectin-1 is involved in the host control of fungi at various body surfaces, including the skin (Kashem et al., 2015), lungs (Werner et al., 2009), vagina (Carvalho et al., 2012), and the GI tract (Carvalho et al., 2012; Iliev et al., 2012; Plantinga et al., 2009) with some

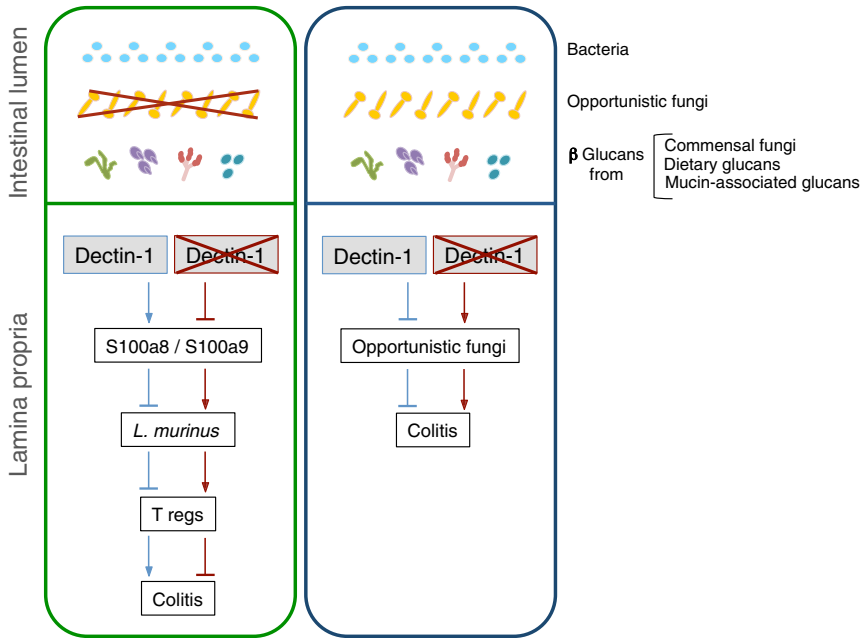

Figure 1. Proposed Model for the Role of Dectin-1 in the Gut
In this issue, Tang et al. (2015) demonstrate that in the absence of opportunistic fungi in the gut, Dectin-1 stimulation by luminal glucans presumably coming from commensal fungi, food, or mucins aggravate experimental colitis in mice. They further show that suppression of Dectin-1 signaling protects mice from experimental colitis by decreasing S100A8 and S100A9 antimicrobial peptide production. This allows the overgrowth of *L. murinus* that trigger T regulatory cell expansion in the gut (left panel). On the other hand, when opportunistic fungi are present in the intestine, absence of Dectin-1 can allow for fungal invasion of the intestinal mucosa and can be detrimental during colitis (right panel). Thus, on one side, Dectin-1 deficiency can have a positive effect on the expansion of bacteria with protective properties, but on the other, it can lead to inability of the host to properly deal with opportunistic fungi in the gut.

discrepancies between specific mouse strains and humans.

Although during fungal overgrowth and infection Dectin-1 has a protective role, there are reports supporting the notion that in models where fungal commensals or pathogens are not present, ligation of Dectin-1 can lead to inflammatory cytokine response and has a detrimental effect to the host (Rosas et al., 2008; Yoshitomi et al., 2005). Therefore, depending on the context, Dectin-1 can protect the host against invading fungi but can also be involved in aggravating inflammation.

In this issue of *Cell Host & Microbe*, Tang et al. (2015) focus on this second aspect and demonstrate that Dectin-1 suppression can ameliorate intestinal inflammation under specific circumstances. They show that in the absence of opportunistic fungal commensals, Dectin-1 can indirectly control bacterial populations in the gut through Dectin-1-dependent anti-microbial peptide (AMP) production. Lack of Dectin-1 signaling can affect AMP production and facilitate the expansion of the gut commensal *Lactobacilli* that are protective during colitis (Figure 1).

Tang et al. (2015) start with a curious observation: that in their mouse colony, mice lacking Dectin-1 (*Clec7a*$^{-/-}$) were more resistant to chemically induced colitis when compared to the wild-type (WT) controls. Transfer of microbiota from conventional SPF *Clec7a*$^{-/-}$ mice into a WT germ-free (GF) host conveyed resistance to chemically induced colitis while specific pathogen-free (SPF) WT microbiota transplantation conferred susceptibility, suggesting Dectin-1-dependent selection for microbiota with "protective" properties. Dectin-1 deficiency itself was not directly involved in this phenotype, as WT GF and *Clec7a*$^{-/-}$ GF mice transferred with WT SPF microbiota experienced similar degree of disease severity.

A recent study demonstrated that mice lacking Dectin-1 exhibit increased susceptibility to colitis, as a result of altered responses to indigenous fungi and invasion of the colonic mucosa by opportunistic fungi such as *Candida* and *Trichosporon* (Iliev et al., 2012). However, *Candida tropicalis*, which was causing the colitis susceptibility in *Clec7a*$^{-/-}$ mice in this former study, was not detected in the mouse colony of Tang et al. (2015). Notably, Tang et al. (2015) showed that upon colonization with *C. tropicalis*, the protection from colitis was completely lost and *Clec7a*$^{-/-}$ mice became highly susceptible to colitis when compared to the WT controls. This suggests a dual role of Dectin-1 in the gut, which is highly dependent on the microbiota makeup (Figure 1).

In attempt to explain the observed *Clec7a*$^{-/-}$ protective phenotype in the absence of opportunistic commensal fungi, the authors next analyzed the bacterial gut microbiota composition in WT and *Clec7a*$^{-/-}$ mice. Upon bacterial 16S deep sequencing analysis, they found a marked increase of *Lactobacillus murinus* in *Clec7a*$^{-/-}$ mice but not in WT controls. *Lactobacillus* species have been recognized as an essential part of a balanced intestinal community and have been shown to participate in the maintenance of protective immunity at the gut and the vaginal mucosa. Therefore, the authors went to investigate whether the increase of *L. murinus* may contribute to colitis protection in *Clec7a*$^{-/-}$ mice. They found that GF mice monocolonized with *L. murinus* followed by WT SPF microflora transfer are protected against colitis when compared to mice colonized only with WT SPF microflora or monocolonized with *Alcaligenes faecalis*—another commensal bacteria found in the mouse colon. This protection was associated with an increase of IL-10-producing CD4^{+} T cells in the colonic lamina propria of these mice. Interestingly, *Clec7a*$^{-/-}$ *Rag2*$^{-/-}$ mice, which lack T and B cells, were not protected from DSS colitis, although *L. murinus* intestinal population was still augmented, suggesting that components of the T or B cell repertoire are responsible for the observed protection. Consistently, increase of *L. murinus* in *Rag2*-sufficient *Clec7a*$^{-/-}$ mice was associated with infiltration of Foxp3^{+} T regulatory (Treg) cells in their colons and protection from colitis. To specifically explore the role of *L. murinus* in Treg cell expansion, GF mice were monocolonized with this strain. Monocolonization with *L. murinus*, but not with *A. faecalis*, led to increased Treg cell infiltration in the

colons, further confirming the link between lactobacilli and Treg cells that might protect mice against colitis.

When SPF WT microflora was transferred into GF mice, *L. murinus* expanded quickly in *Clec7a*$^{-/-}$ GF host but not in the WT GF mice, suggesting Dectin-1-dependent control of lactobacilli. How does Dectin-1 influence the size of lactobacilli population in the gut? After excluding the possibility of a direct recognition of *L. murinus* by Dectin-1, the authors explored an indirect mechanism of lactobacilli population control by this receptor. One possible scenario is that Dectin-1 stimulation can influence local immunity and indirectly affect lactobacilli. The authors explored this possibility further and found that the absence of Dectin-1 is associated with decreased AMP production in the intestines of *Clec7a*$^{-/-}$ mice. They also found that *L. murinus* was susceptible to S100A8 and S100A9, two AMPs that were reduced in the colons of *Clec7a*$^{-/-}$ mice. Furthermore, blockage of Dectin-1 signaling in WT SPF mice by the soluble β-glucan laminarin ameliorated colitis and was associated with reduced AMP production and increased *L. murinus* in the intestine of these mice. This suggested that Dectin-1 blockage might be protective during colitis through inhibition of AMP production and expansion of potentially beneficial bacteria in the colon. Finally, *Lactobacillus salivarius*, a strain that is closely related to the murine *L. murinus*, was reduced in the feces of patients with Crohn's disease, demonstrating that intestinal disease and related dysbiosis affects the lactobacilli population also in humans.

Overall, Tang et al. (2015) reveal a role for Dectin-1 in indirect control of lactobacilli in the gut; however, some questions remain. What will be the consequence of Dectin-1 suppression when opportunistic commensal fungi are present in the gut? *Candida* species are commonly found in the human intestine, and potential therapeutic suppression of Dectin-1 might be a double-edged sword: on one side, it might have a positive effect on the expansion of bacteria with protective properties, but on the other, it can lead to inability of the host to properly deal with opportunistic fungi in the gut. Although *C. tropicalis* was absent in the mouse colony used in the present study, Dectin-1 stimulation by other commensal fungi in the intestinal lumen cannot be excluded. Despite some challenges, the next-generation sequencing technologies have allowed for deeper exploration of host-associated mycobiota and have prompted recent efforts in the development of bioinformatics tools and databases for "mycobiome" characterization and analysis. Therefore, such improved tools can be used to further characterize the gut mycobiota in various *Clec7a*$^{-/-}$ mouse colonies. In addition to commensal fungi, future studies need to explore the relative contribution of other Dectin-1 ligands in the gut, such as intestinal mucin-associated or dietary glucans that might affect Dectin-1-dependent AMP production. What is the mechanism by which Dectin-1 induces AMP production and which are the mediators of this phenomenon? Although Tang et al. (2015) show that intestinal epithelial cells (IECs) express low levels of Dectin-1, others have demonstrated that IECs can respond to β-glucans. It is also possible that Dectin-1-expressing immune cells that are sensing β-glucans in the lamina propria can affect AMP production through crosstalk with IECs. Does Dectin-1-dependent AMP production influence other Gram-positive bacteria, and can Dectin-1 suppression predispose the host to infection with specific Gram-positive pathogens? Finally, are there other cells besides Tregs that are influenced by lactobacilli and might contribute to the protective phenotype during Dectin-1 deficiency?

Despite some questions that still need to be addressed in the future, the study of Tang et al. (2015) provides an important insight on the role of Dectin-1 in mucosal immunity and underscores the dual control that this receptor exerts on fungal and bacterial communities in the gut.

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